Using the BLT Humanized Mouse as a Stem Cell based Gene Therapy Tumor Model.

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Public Summary:

Scientific Abstract:
Small animal models such as mice have been extensively used to study human disease and to develop new therapeutic interventions. Despite the wealth of information gained from these studies, the unique characteristics of mouse immunity as well as the species specificity of viral diseases such as human immunodeficiency virus (HIV) infection led to the development of humanized mouse models. The earlier models involved the use of C. B 17 scid/scid mice and the transplantation of human fetal thymus and fetal liver termed thy/liv (SCID-hu) (1, 2) or the adoptive transfer of human peripheral blood leukocytes (SCID-huPBL) (3). Both models were mainly utilized for the study of HIV infection. One of the main limitations of both of these models was the lack of stable reconstitution of human immune cells in the periphery to make them a more physiologically relevant model to study HIV disease. To this end, the BLT humanized mouse model was developed. BLT stands for bone marrow/liver/thymus. In this model, 6 to 8 week old NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ (NSG) immunocompromised mice receive the thy/liv implant as in the SCID-hu mouse model only to be followed by a second human hematopoietic stem cell transplant (4). The advantage of this system is the full reconstitution of the human immune system in the periphery. This model has been used to study HIV infection and latency (5-8). We have generated a modified version of this model in which we use genetically modified human hematopoietic stem cells (hHSC) to construct the thy/liv implant followed by injection of transduced autologous hHSC (7, 9). This approach results in the generation of genetically modified lineages. More importantly, we adapted this system to examine the potential of generating functional cytotoxic T cells (CTL) expressing a melanoma specific T cell receptor. Using this model we were able to assess the functionality of our transgenic CTL utilizing live positron emission tomography (PET) imaging to determine tumor regression (9). The goal of this protocol is to describe the process of generating these transgenic mice and assessing in vivo efficacy using live PET imaging. As a note, since we use human tissues and lentiviral vectors, our facilities conform to CDC NIH guidelines for Biosafety Level 2 (BSL2) with special precautions (BSL2+). In addition, the NSG mice are severely immunocompromised thus, their housing and maintenance must conform to the highest health standards (http://jaxmice.jax.org/research/immunology/005557-housing.html).